REMARKS

Claims 13, 61-67, 70, and 76 are pending in this application upon entry of the claim amendments presented herein. Claims 68, 71-73, 75, 77, and 79 are currently withdrawn from consideration. These claims are not canceled from this application because a request for rejoinder, if appropriate, will be filed at a later time.

Claim 13 is amended to add the phrase "having said disorder." Further, claim 13 is amended to correct a typographical error, *i.e.*, to replace "(S,S)-2-(3-chlorophenyl)-3,5,5-trimethyl-3-morpholinol" with "(S,S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol." Support can be found, for example, on page 2, scheme 2 and page 8, line 31-page 9, line 2 of the specification.

Claims 61-67 and 76 are amended to correct the same typographical error. No new matter has been added.

Applicants respectfully submit that the pending claims are allowable at least for the following reasons.

I. The Rejection Under 35 U.S.C. § 112 Should be Withdrawn.

Claims 13 and 61-67 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention." (Office Action, page 3). It appears that this rejection stems from the misspelling of the chemical compound recited by the claims.

In this regard, claims 13, 61-67, and 76 are amended to replace "(S,S)-2-(3-chlorophenyl)-3,5,5-trimethyl-3-morpholinol" with "(S,S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol." In view of this amendment, Applicants respectfully request that this rejection be withdrawn.

II. The Rejection Under 35 U.S.C. § 102(e) Should be Withdrawn.

On pages 3-5 of the Office Action, claims 13, 61-67, 70 and 76 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Morgan *et al.*, U.S. Patent No. 6,274,579 ("Morgan"). In particular, while the Examiner acknowledges that Morgan is silent about

treating bipolar or manic condition, it is alleged that the claimed invention is anticipated because "it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure." (Office Action, page 4). Applicants respectfully traverse this rejection.

It is well settled that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (MPEP §2131 (*citing Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987)) (emphasis added)).

In this regard, Applicants respectfully submit that the Office Action's reliance on *In re Woodruff* in rejecting claims 13, 61-67, 70 and 76 as anticipated by Morgan is misplaced. (*See* Office Action, page 4). Specifically, it is alleged in the Office Action that the claims are anticipated based on the assertion that Applicants are "claiming a new benefit of an old process. . . ." (*Id.*). However, Applicants respectfully submit that the claimed method is not an old process because treating bipolar or manic condition by administering to a patient a therapeutically effective amount of optically pure (S,S)-2-(3-chlorophenyl)-3,5,5,-trimethyl-2-morpholinol ("(S,S)-hydroxybupropion"), or a pharmaceutically acceptable salt, solvate, or clathrate thereof, was not known. As correctly recognized by the Examiner, Morgan does not teach the claimed method of treating bipolar or manic condition. (*Id.*). Thus, since "each and every element as set forth in the [instant] claim" is not found in a single prior art reference, Applicants respectfully submit that the claim rejection should be withdrawn. (MPEP §2131 (*citing Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987)) (emphasis added)).

III. The Rejection Under 35 U.S.C. § 103(a) Should be Withdrawn.

Applicants appreciate the Examiner's withdrawal of the rejection under 35 U.S.C. § 103(a) as being unpatentable over Simeon *et al.*, *Canadian Journal of Psychiatry*, 31(6): 581-5 (1986) in view of Morgan, which was raised in the previous office action. However, a new ground(s) of rejection of claims 13, 61-67, 70, and 76 was made under 35 U.S.C. § 103(a) as being allegedly unpatentable over Morgan in view of the abstract of Gelenberg *et al.*, *Report on efficacy of treatments for bipolar disorder*, 29(4) Psychopharmacol Bull. 447, 447-56

(1993) ("Gelenberg"). (Office Action, pages 5-7). Applicants respectfully traverse this rejection.

The standard for obviousness under 35 U.S.C. §103 was recently clarified in the landmark decision of *KSR International Co. v. Teleflex Inc.* (127 S.Ct. 1727, 167 L.Ed.2d 705, 75 USLW 4289, 82 U.S.P.Q.2d 1385 (2007)). In *KSR*, the Supreme Court held that the application of the "teaching, suggestion, motivation" test is not mandatory in determinations of obviousness under 35 U.S.C. §103 and cautioned against the use of "rigid and mandatory formulas." (*Id.* at 1741). However, the Court nonetheless emphasized that determinations of obviousness based on hindsight analysis is still improper. Indeed, the Court warned that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." (*Id.*). As the Court explained, this is because "inventions in most, if not all instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*Id.*). As such, the Court stated that the TSM test "captured a helpful insight" because it is important "to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does." (*Id.*).

In light of this holding, in decisions following *KSR*, the Federal Circuit and District Courts have required a showing that one skilled in the art would have had a reason to combine or modify prior art elements in determinations of obviousness under 35 U.S.C. §103. (*See, e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007) (Patent challenger alleging obviousness must show "by clear and convincing evidence that a person of ordinary skill in the art would have had reason to make the composition of device, or carry out the claimed process...."); *Takeda Chemical Industries, Ltd. v. Alphapharm Pty.*, Ltd. 492 F.3d 1350 (C.A.Fed. (N.Y.)), 83 U.S.P.Q.2d 1169 (Fed. Cir. 2007) ("[I]t remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."); *Bayer AG v. Dr. Reddy's Labs, Inc.*, 2007 WL 3120794 (D. Del. 2007) (Chemical composition claims held to be unobvious in part because defendant did not show "by clear and convincing evidence, that a person of ordinary skill in the art would have had a reason to attempt to make the claimed compositions....")).

Further, as the Supreme Court in *KSR* explained, an obviousness determination takes into account whether the combination of elements would yield "anticipated success" or "predictable results." (*Id.* at 1739).[1] As such, following the *KSR* decision, the Federal Circuit has based determinations of obviousness on whether a claimed combination would have yielded "predictable results" or whether there would have been "a reasonable expectation of success" in the claimed invention. (*See, e.g., In re Trans Tex. Holdings Corp*, 498 F.3d 1290 (Fed. Cir. 2007) (determination of obviousness for a patent relating to stem cell research based on whether the combination yielded "predictable results"); *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007) (patent challenger must show by "clear and convincing evidence" that there would have been a "reasonable expectation of success"); *Aventis Pharma Deutschland GmbH v. King Pharms, Inc.* 499 F.3d 1293, 1301 (Fed. Cir. 2007) (determination of obviousness based on whether the prior art provided an "expectation" that claimed compounds would have the intended properties)). The District Courts have also taken the same approach. (*See, e.g., Friskit Inc. v. Real Networks, Inc.*, 499 F.Supp2d 1145 (N.D. Cal. 2007) (analysis under 35 U.S.C. §103 for patent related to streaming content based on whether prior art elements were "integrated...to produce a result which was predictable."); *Boston Scientific Corp. v. Johnson & Johnson*, 2007 WL 2408870 (N.D. Cal. 2007) (Defendant's summary-judgment motion of obviousness for patent relating to catheters denied in part because "[i]t is unclear whether [the prior art] presented such a viable solution so as to yield predictable results") (internal quotations omitted)).

The Federal Circuit, following *KSR*, articulated guidelines for determining "whether the expectation of success from a particular line of inquiry is great enough to render a resulting invention obvious." (*PharmaStem*, 491 F.3d at 1364). As the Federal Circuit explained:

> [A]n invention would not be invalid for obviousness if the inventor would have been motivated to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as

[1] The Court also noted that while a showing that a combination was obvious to try "might" be sufficient for a conclusion of obviousness, the Court conditioned such a conclusion on a showing of "anticipated success." (*Id.* at 1742 (emphasis added); *see also* MPEP §2145(X)(B)).

> to which of many possible choices is likely to be successful. Likewise, an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

(*Id.* (citing *In re O'Farrell*, 953 F.2d 894, 903 (Fed.Cir. 1988)) (internal quotations omitted)).

In sum, on the basis of *KSR* and the Federal Circuit and District Court cases following *KSR*, the current standard of obviousness takes into account: (1) whether there would have been a "reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does;" and (2) whether the combination of elements would have yielded "predictable results" *i.e.*, whether there would have been a reasonable expectation of success. (*See e.g., PharmaStem* 491 F.3d at 1360 ("The burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so.") (emphasis added, internal quotations omitted)).

In the instant case, the Office alleges that claims 13, 61-67, 70, and 76 are unpatentable because it would have been obvious "to incorporate (S,S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol, which is an active metabolite buporpion, for the treatment of bipolar or manic condition." (Office Action, page 6). Applicants respectfully submit, however, that no *prima facie* case of obviousness is established by the references cited in the Office Action. Specifically, Applicants respectfully submit that: (1) no reason that would have prompted a person skilled in the art to combine the teachings of the cited references to arrive at the claimed method is provided in the Office Action; and (2) the combined teachings of cited references would not have provided the requisite expectation of success in the instant claims.

1. There would have been no reason for a person skilled in the art to combine the teachings of the cited references to arrive at the claimed method.

In the Office Action, it is alleged that one skilled in the art would have been motivated to incorporate (S,S)-hydroxybupropion for the treatment of bipolar or manic condition because of "the possibility of improved therapeutic effectiveness and safety by

reduction of side effects due to lower dose usage for the same outcome. . . ." (Office Action, page 6). Applicants respectfully disagree.

Applicants respectfully point out that Morgan does not give a sufficient reason that would have prompted those of ordinary skill in the art to replace bupropion with (S,S)-hydroxybupropion. In this regard, Applicants respectfully point out that, although Morgan reports that the anti-depressant activity of racemic bupropion is likely to result from (S,S)-hydroxybupropion, it does not provide any disclosure or suggestion that bupropion may be replaced with (S,S)-hydroxybupropion in any and all methods where bupropion is used.

For example, Morgan discloses that, while (S,S)-hydroxybupropion "was approximately twice as potent as [racemic bupropion] as an NA inhibitor," it was "approximately 10-fold less potent as an inhibitor of dopamine uptake." (Morgan, col. 7, lines 25-29). Therefore, at most, Morgan merely shows that (S,S)-hydroxybupropion has different, but not necessarily more desirable, pharmacological properties than racemic bupropion. Thus, Morgan sets forth a list of specific disorders against which (S,S)-hydroxybupropion may be used, none of which is a disorder recited by the pending claims. (*See* Morgan, Abstract and col. 2, lines 46-63).

Further in this regard, Morgan clearly discloses that "the mechanism of action of bupropion, as with other antidepressants, is unknown." (Morgan, col. 1, lines 24-25) (emphasis added). Therefore, by disclosing that bupropion's mechanism of action was not well-understood, and that (S,S)-hydroxybupropion has properties merely different than those of bupropion, Morgan certainly would not have taught or suggested to those skilled in the art a reason that (S,S)-hydroxybupropion can replace bupropion in all of the uses contemplated for bupropion, much less in the methods recited by the pending claims.

Gelenberg does not cure the defects of Morgan because there is nothing in Gelenberg that would lead one skilled in the art to replace bupropion with (S,S)-hydroxybupropion. In addition, Gelenberg does not provide a sufficient reason that would have prompted one skill in the art to select bupropion, let alone (S,S)-hydroxybupropion, from the list of agents disclosed in Gelenberg for the treatment of bipolar or manic condition. As is well settled, the legally required "reason" to select a species or subspecies from a genus for purposes of 35 U.S.C. §103 does not exist unless there was "[s]ome motivation to select the claimed species

or subgenus [from] the prior art." (MPEP §2144.08; *see also In re Deuel*, 51 F.3d 1552, 1558-9, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995) ("No particular one of these DNA's can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared.") (emphasis added); *In re Baird*, 16 F.3d 380, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994) ("Absent anything in the cited prior art suggesting which of the 10^{36} possible sequences corresponds to [a gene], the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences.")).

In this regard, Gelenberg discloses a number of agents that have been successful in treating acute bipolar depression. (Gelenberg, page 447). For example, these agents include "monoamine oxidase inhibitors (e.g., tranylcypromine), lithium, tricyclic antidepressants, and second-generation antidepressants (e.g., bupropion), . . . [electroconvulsive therapy], sleep deprivation, and light therapy. . . ." (*Id.*). Thus, Gelenberg discloses a very large number of agents, any one of which could have been selected as a lead agent for further study. While Gelenberg discloses bupropion as an example for second-generation heterocyclic antidepressants, Gelenberg does not provide anything regarding the desirability of singling out bupropion from the long list of disclosed agents. (Gelenberg, page 451). Similar to *Baird*, absent such a disclosure, Applicants respectfully point out that the burden of establishing that the prior art would have prompted those skilled in the art to single out bupropion, much less (S,S)-hydroxybupropion, is not met in the Office Action. Thus, since a *prima facie* case of obviousness cannot be established without such a showing, Applicants respectfully submit that the obviousness rejection should be withdrawn for this reason alone.

Furthermore, Applicants respectfully point out that the claimed invention is even more unobvious because Gelenberg actually teaches away from using bupropion, let alone the claimed metabolite, to treat bipolar depression. In this regard, Applicants respectfully point out that in *Yamanouchi Pharmaceutical Co. Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1344-45, 56 U.S.P.Q.2d 1641 (Fed. Cir. 2000), the Federal Circuit held that the selection of a compound as a lead compound for drug development was not obvious even though the compound exhibited activity that was three times greater than the benchmark compound. In explaining its holding, the Court focused on the disclosure of better alternatives that were up to ten times more active than the benchmark compound and held that the required motivation was not shown. (*Id.*). Therefore, the court implied that the

claimed subject matter is non-obvious where there were alternatives that were presumably "better" than the claimed subject matter at the time of the invention. (*See* i*d.* at 1345).

In this regard, Applicants respectfully submit that the Office Action fails to consider Gelenberg as a whole, which teaches several better alternatives to bupropion. (*See, e.g.*, MPEP, §2141, *citing W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) ("A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the invention.") (emphasis in original)). While Gelenberg discloses bupropion as an example of second-generation heterocyclic antidepressants, Gelenberg discloses that better alternatives to antidepressants existed at the time of this application. (Gelenberg, page 451). For example, Gelenberg cites a study that compared electroconvulsive therapy ("ECT") with simulated ECT, placebo, a tricyclic antidepressant, or a monoamine oxidase inhibitor in patients with depression who had not responded well to previous studies with antidepressants. (*Id.*). The study found "ECT to be superior to the other four treatments: overall efficacy rates were approximately 78 percent for ECT . . . ," clearly indicating that ECT was deemed a better alternative to other compounds tested, including an antidepressant. (*Id.*) (emphasis added). Thus, Applicants respectfully submit that those skilled in the art, reading Gelenberg, would have been led away from bupropion because better alternatives to bupropion administration (*e.g.*, ECT) to patients with depression are clearly taught by Gelenberg. Consequently, to the extent that Gelenberg actually teaches away from the currently claimed methods, Applicants respectfully point out that the claims are not obvious over Morgan and Gelenberg.

For at least these reasons, Applicants respectfully submit that claims 13, 61-67, 70, and 76 are not obvious, and thus, request that their rejection be withdrawn.

2. The claimed invention is even more unobvious because the combined teachings of Morgan and Gelenberg would not have provided the requisite expectation of success.

It is alleged in the Office Action that one skilled in the art would have had a reasonable expectation of successfully using (S,S)-hydroxybupropion for the treatment of bipolar or manic condition "because bupropion and its metabolites utilize the same pathways

to obtain the same pharmacological effect." (Office Action, page 6-7). Applicants respectfully disagree.

Applicants respectfully point out that the reasoning provided in the Office Action is factually and scientifically incorrect. As discussed above, Morgan itself discloses that the pharmacological effects of bupropion and (S,S)-hydroxybupropion are different. (*See* page 10, above). Further, Morgan certainly does not provide any disclosure or suggestion that bupropion may be replaced with (S,S)-hydroxybupropion in any and all methods where bupropion is used. Consequently, it is evident from the disclosure of Morgan that the allegations made in the Office Action that "bupropion and its metabolites utilize the same pathways to obtain the same pharmacological effect" is incorrect. (Office Action, page 7). To the extent that the allegation of reasonable expectation of success is based on this incorrect proposition, and in view of the fact that no other reasoning or evidence to support the reasonable expectation of success is provided in the Office Action, Applicants respectfully submit that no *prima facie* case of obviousness is established. Thus, Applicants respectfully request that the rejection of the claims be withdrawn for this additional reason.

IV. Conclusion

For at least the foregoing reasons, Applicants respectfully submit that all of the pending claims are in allowable condition, and thus request that the rejection of the pending claims be withdrawn.

No fee, other than a fee of $120 for extension of time, is believed due for this submission of the Petition for Extension of Time submitted herewith. However, should any additional fees be due for this submission or to avoid abandonment of the application, please charge such fees to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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